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UNITED STATES PATENT APPLICATION

of

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for

A GIGAMATRIX HOLDING TRAY HAVING THROUGH-HOLE WELLS

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5 The present application is a continuation-in-part of pending U.S. Patent Application Serial No. 09/894,956 filed June 27, 2001, which is a continuation-in-part of pending U.S. Patent Application Serial No. 09/687,219, filed October 12, 2000, which is a continuation-in-part of pending U.S. Patent Application Serial No. 09/444,112, filed November 22, 1999, which is a continuation-in-part of pending U.S. Patent Application Serial No. 08/876,276, filed June 16, 1997; additionally, the present application is a continuation-in-part of pending U.S. Patent Application Serial No. 09/636,778, filed August 11, 2000, which application is a continuation and claims the benefit of priority under 35 U.S.C. 10 § 120 of U.S. Patent Application Serial No. 09/098,206, filed June 16, 1998, which issued as U.S. Patent No. 6,174,673 on January 16, 2001, which is a continuation-in-part of pending U. S. Patent Application Serial No. 08/876,276, filed June 16, 1997, all of the contents of which are incorporated by reference in their entirety herein.

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#### FIELD OF THE INVENTION

20 The present invention pertains particularly to plates for holding a large number of relatively small-volume fluid samples. More particularly, the present invention pertains to plates that are formed with a plurality of through-hole wells in which individual samples can be held. The present invention is particularly, but not exclusively, useful as a GigaMatrix<sup>TM</sup> plate that has a relatively large number of through-hole wells with relatively high aspect ratios, wherein each through-hole well can be optically distinguished from other through-hole wells in the plate.

## BACKGROUND OF THE INVENTION

Plates or trays for holding assays or specimen samples in a fluid solution can be generally grouped into either one of two different types of devices. One type is formed with depressions or wells which have bottoms that support the assay or specimen while it is being processed. The other type incorporates through-hole wells that rely on surface tension to hold the fluid assay or sample in the through-hole well during processing. For example, U.S. Patent No. 6,027,873 which issued to Schellenberger et al. for an invention entitled "Multi-Through Hole Testing Plate for High Throughput Screening" discloses a holding or testing plate of this second type. Not surprisingly, however, it happens that both types of holding plates have their respective advantages and disadvantages.

Insofar as holding plates having through-hole wells are concerned, one advantage they have is that they can be easily filled. Specifically, this can be done by simply immersing a surface of the holding plate into a solution to be analyzed. The through-hole wells are then filled with the solution by capillary action. This, in turn, leads to another advantage which is that a very large number of relatively small volume solution samples can be simultaneously prepared, but individually assayed.

As stated above, in addition to their advantages, sample holding plates also have their disadvantages. In particular, there is a significant disadvantage to presently available holding plates with through-hole wells. This disadvantage stems from the fact that the through-hole wells of presently available holding plates have aspect ratios (i.e. a ratio of the length of the well to its inner diameter) that are generally less than 5:1. Accordingly, a significant portion of the solution sample in the through-hole well is exposed to the environment. A consequence of this is that, due to evaporation, such plates can effectively support solution samples for only relatively short periods of time (e.g. minutes or a few hours). The present invention recognizes that

through-hole wells having aspect ratios greater than 5:1 can effectively diminish the consequences of evaporation.

In addition to the advantages noted above, an attribute that is desirable for all types of holding plates is that they provide the ability to properly process the assays (samples) that are being held by the plate. Specifically, in some instances, it may be desirable or necessary to observe any changes in the sample that take place while it is being held by the plate. Such changes, however, may require several days, or even longer. In the particular case of holding plates with through-hole wells, the observation techniques that are being used must effectively account for the small volumes of the solution samples and their close proximity to each other on the holding plate. If optical techniques are used for these purposes, the individual through-hole wells of the holding plate must also be optically distinguishable.

In light of the above, it is an object of the present invention to provide a GigaMatrix holding plate with through-hole wells that have relatively high aspect ratios (e.g. greater than 5:1) to limit the effects of evaporation to approximately five percent of solution sample volume per day (5%/day). Another object of the present invention is to provide a GigaMatrix holding plate which allows respective through-hole wells to be optically distinguishable. Still another object of the present invention is to provide a GigaMatrix plate for holding a large number of small volume samples that is easy to use, relatively simple to manufacture and comparatively cost effective.

#### SUMMARY OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, a GigaMatrix plate for holding a large number of relatively small solution samples includes a base having a first surface and an opposed second surface that is substantially parallel thereto. Open-ended capillary tubes extend through the base between its first and second surfaces to establish a plurality of substantially parallel through-hole wells. As envisioned for the present invention, the GigaMatrix holding plate can have in excess of a thousand such through-hole wells.

Each tube in the holding plate of the present invention has an interior surface that defines a lumen. This lumen further defines a longitudinal axis for the tube. Importantly, each tube has an aspect ratio (i.e. a ratio of lumen diameter to length of tube) that is greater than about 5:1. Within the parameters of such an aspect ratio, the lumen of each tube will have an inner diameter that is less than approximately five hundred microns, and a length that is greater than about five millimeters.

A contemplation of the present invention is that the plate will be used for holding samples in respective capillary tubes, and that these samples will fluoresce under appropriate conditions. With this in mind, it is an important aspect of the present invention that the holding plate be structured so that whenever a sample in a tube lumen is excited to become fluorescent, each tube will be independently and optically distinguishable from other tubes in the holding plate.

The structure of each tube in the holding plate can be made of a sleeve glass which is embedded in an interstitial material that holds the various tubes of the holding plate together on the base. For each tube, the sleeve glass surrounds the lumen of the tube. In one embodiment of the present invention, the sleeve glass itself is surrounded by a black, extra mural absorption (EMA) glass which absorbs most of the fluorescent light that is directed from the sample toward the tube. In another embodiment, the sleeve glass itself is heat-treated to make it effectively opaque and, thus, light absorptive for the above stated purposes. In yet another embodiment, the sleeve glass and interstitial material can be the same. Further, the glass in this last embodiment may be clear glass, but it should have refractive properties which make each tube optically distinguishable.

Additional aspects of the present invention include the fact that the interior surface of each tube lumen can be coated to control the tube's capillary action, or to provide a surface chemistry in the lumen. Also, a reference indicia can be established on the base of the plate for purposes of positioning and aligning the base, as required.

## BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of this invention, as well as the invention itself, both as to its structure and its operation, will be best understood from the accompanying drawings, taken in conjunction with the accompanying description, in which similar reference characters refer to similar parts, and in which:

Fig. 1 is a perspective view of a GigaMatrix plate in accordance with the present invention;

Fig. 2A is a top plan view of a portion of the GigaMatrix plate showing one embodiment of a through-hole well for the present invention;

Fig. 2B is a top plan view of a portion of the GigaMatrix plate showing an alternate embodiment of a through-hole well;

Fig. 3A is a cross sectional view of the through-hole well shown in Fig. 2A as would be seen along the line 3-3 in Fig. 1;

Fig. 3B is a cross sectional view of the through-hole well shown in Fig. 2B as would be seen along the line 3-3 in Fig. 1;

Fig. 4 is a perspective view of an optical fiber that would be suitable for use in manufacturing through-hole wells for the GigaMatrix plate of the present invention;

Fig. 5 is a perspective view of the optical fiber shown in Fig. 4 after it has been drawn down;

Fig. 6A is a perspective view of multis created by stacking sections of the drawn optical fiber shown in Fig. 5; and

Fig. 6B is a perspective view of assembled multis for use in manufacturing the GigaMatrix plate of the present invention.

## DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring initially to Fig. 1, a GigaMatrix plate in accordance with the present invention is shown and is generally designated 10. As shown, the

plate 10 includes a base 12 having a generally flat upper surface 14 and an opposed, also generally flat, lower surface 16. Reference indicia, such as the bumps or rises 18a and 18b shown in Fig. 1, can be used to orient and align the plate 10 as necessary during its use. Most importantly, however, is the fact that the plate 10 is formed with a plurality of through-hole wells 20 that extend through the base 12 between the upper surface 14 and the lower surface 16. As envisioned for the present invention, these through-hole wells 20 are all substantially parallel to each other, and they have a density of approximately two through-hole wells 20 per square millimeter of area on the surfaces 14, 16.

It is an important aspect of the present invention that the plate 10 be formed with a plurality of through-hole wells 20. For the present invention, this plurality may include as many as a thousand or more such wells 20. Structurally, the through-hole wells 20 are preferably any one of three possible embodiments. The first such embodiment, shown as the through-hole well 20' in Fig. 2A, is formed with a lumen 22 that is surrounded and defined by the interior surface 24 of an interior wall 26. Additionally, the through-hole well 20' (Fig. 2A) includes an outer wall 28 that surrounds the interior wall 26. For the second embodiment, shown as the through-hole well 20" in Fig. 2B, there is no outer wall 28. The difference in these structures, as more fully disclosed below, stems from the optical characteristics exhibited by the interior wall 26. Regardless, for both of these embodiments, the plate 10 includes an interstitial material 30 in which the through-hole well 20' (or 20") is embedded and held together in the base 12 with the other through-hole wells 20 of the plate 10. For the third embodiment, the interior wall 26, outer wall 28 and interstitial material 30 may all be the same.

As mentioned above, differences between the various embodiments for through-hole well 20 are dependent on the optical properties of their respective interior walls 26. For the through-hole well 20' (Fig. 2A) the interior wall 26 is preferably made of a sleeve glass that is of a type well known in the pertinent art. This sleeve glass alone, however, may not have the light absorptive properties that are preferred for the plate 10. If so, the outer wall

28 can be added and used to achieve the desired result. For this purpose, the outer wall 28 is preferably made of an extra mural absorptive (EMA) glass. On the other hand, for the through-hole well 20" (Fig. 2B) it is possible that the interior wall 26 be made of a sleeve glass which, after being heat-treated, will become substantially opaque. In either of these two cases, it is preferable that the through-hole wells 20 (either 20' or 20") have light absorptive characteristics that will minimize "cross-talk" (i.e. light interference) between adjacent through-hole wells 20 in the plate 10. Furthermore, if the inner wall 26, outer wall 28 and interstitial material 30 are all the same, it is important that the refractive properties of the material be such that the individual lumens 22 of the through-hole wells 20 can be optically distinguished from the material of the holding plate 10.

Dimensionally, the through-hole wells 20 of the plate 10 have several salient aspects. In all, there are two paramount aspects of the plate 10 that are particularly important. First is that the through-hole wells 20 function as capillary tubes that can be effectively filled by a wicking action. Second, and of equal importance, is that the through-hole wells 20 be configured to minimize the effects of evaporation. For the plate 10 of the present invention, both of these aspects are addressed by properly dimensioning the configuration of the through-hole wells 20.

As perhaps best appreciated by cross referencing Figs. 2A and 2B with Figs. 3A and 3B, the through-hole wells 20 are preferably cylindrical in shape and define a longitudinal axis 32 (Fig. 3A). The cross-section of the through-hole wells 20, however, may be oval or rectangular. With these structures, each through-hole well 20 has a length 34 and an inner diameter 36. Specifically, the inner diameter 36 is the diameter of lumen 22. Importantly, these dimensions define an aspect ratio, "A", that for a through-hole well 20 is the ratio of its length 34 to its diameter 36. As intended for the present invention, "A" will be greater than approximately 5:1, and may be as much as 30:1, or more. Within the values of these parameters for "A", the length 34 is preferably in a range of about five to ten millimeters (5-10 mm) and the inner



10084552-022502

diameter 36 of the through-hole well 20 is preferably less than about five hundred microns (500  $\mu\text{m}$ ).

Manufacturing a GigaMatrix plate 10 in accordance with the present invention begins by providing a single elongated optical fiber 38, such as shown in Fig. 4. Specifically, the optical fiber 38 will have an initial length 40, and will include a cylindrical shaped core glass 42 that is surrounded by a concentric layer of sleeve glass. More specifically, this sleeve glass will eventually comprise the interior wall 26 of a through-hole well 20. As shown in Fig. 5, the outer wall 28, if used, and the interstitial material 30, in all instances, will be included in the optical fiber 38.

Once an optical fiber 38 has been selected, it is drawn down in a manner well known in the pertinent art to create an optical fiber having a length 44. As will be appreciated by comparing Fig. 4 with Fig. 5, the length 44 is much longer than the length 40. The drawn optical fiber 38 (Fig. 5) is then cut into a plurality of sections 46, of which the sections 46a, b, c,...w and x are only exemplary. Next, the individual sections 46 are stacked together to create a so-called multi 48. As best seen with reference to Figs. 6A and 6B, the sections 46 are stacked together in a substantially parallel arrangement, such as shown for the exemplary multis 48a and 48b. After the multis 48 have been created, they are then pressed together as indicated by the arrow 50, and heated to fuse the interstitial material. Although only the multis 48a and 48b are shown in Fig. 6A, it is to be appreciated that many such multis 48 can be fused together. Also, the process can be repeated to create multi-multis. Regardless how the multis 48 are made, the result is a unit assembly 52 that serves as a precursor for the plate 10.

After a plurality of the multis 48 have been pressed together, the resultant unit assembly 52 is carefully heated to fuse the interstitial material 30 between adjacent sections 46. For example, in order to avoid structural damage to materials in the unit assembly 52, this heating may be accomplished at relatively slow rates. Specifically, this is done to bond the sections 46 into an integral unit assembly 52. After cooling, the unit assembly 52 is cut and ground to establish a substantially same predetermined length

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for each of the sections 46. As a consequence of this, the surfaces 14 and 16 of the plate 10 are created with a distance between them that is preferably about six millimeters.

5 An important step in the manufacture of the GigaMatrix plate 10 of the present invention is that, after the unit assembly 52 has been cut and its surfaces 14 and 16 smoothed by grinding, the whole assembly 52 is immersed into an acid bath (not shown). This is specifically done to etch the core glass 42 from the assembly 52 to create the GigaMatrix plate 10. For the embodiment of plate 10 wherein the through-hole well 20" does not include the outer wall 28 of EMA glass, a final step in the manufacture of plate 10 can require heat-treating the plate 10 to make the sleeve glass of interior wall 26 substantially opaque.

10 In use, a surface 14 or 16 of the plate 10 is immersed into a container (not shown) that is holding samples 54 in a liquid solution 56. As intended for the present invention, this action wicks the samples 54 along with the liquid solution 56 into the through-hole wells 20 by a capillary action. The samples 54 are then held in the through-hole wells 20 to be subsequently assayed. Although the aspect ratio "A" that is manufactured for the through-hole wells 20 of plate 10 will act to minimize the effects of evaporation, this feature of the present invention can be supplemented. Specifically, as shown in Fig. 3B, a cap 58 can be used to cover the through-hole wells 20. Alternatively, a membrane (not shown) can be used for this purpose. Also, a wax, or a high vapor pressure fluid 60, can be inserted into the through-hole wells 20 to retard evaporation. Further, an obvious step for further reducing the effects of evaporation on the liquid solution 56 is to place the plate 10 in a humidified environment.

20 With the construction of the plate 10 as disclosed herein, it is possible to detect individual samples 54 in separate through-hole wells 20 if the samples 54 can be somehow excited to be fluorescent. Specifically, due to the light absorptive characteristics of the outer wall 28, or an appropriately heat-treated interior wall 26, each through-hole well 20 (capillary tube) will act as a light channel. On the other hand, to a lesser degree, the material of the

holding plate 10, by itself, can have refractive properties that will allow the individual lumens 22 in the plate 10 to be optically distinguishable. With reference back to Fig. 3A, it can be seen that when fluorescent light is emitted by the sample 54, and is directed toward the interior surface 24 of the lumen 22, (e.g. as indicated by the arrow 62), the light will be refracted by the outer wall 28. One important consequence of this is that this refracted light can be distinguished from the light that is emitted from sample 54 and directed along the axis 32 will emerge from the through-hole well 20 (e.g. as indicated by the arrow 64). This light can then be used for the optical detection of the sample 54. Also, this light is sufficient to optically distinguish the particular through-hole well 20 in which the sample 54 is located from adjacent through-hole wells 20.

While the particular GigaMatrix Holding Tray Having Through-Hole Wells as herein shown and disclosed in detail is fully capable of obtaining the objects and providing the advantages herein before stated, it is to be understood that it is merely illustrative of the presently preferred embodiments of the invention and that no limitations are intended to the details of construction or design herein shown other than as described in the appended claims.